Valence-dependent disruption in processing of facial expressions of emotion in early visual cortex − a TMS study

Kun Guo, Lauren Calver, Yoshi Soornack, Patrick Bourke

School of Psychology, University of Lincoln, Lincoln LN6 7TS, UK

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Corresponding author:

Prof. Kun Guo

School of Psychology, University of Lincoln, Brayford Pool, Lincoln LN6 7TS, UK

e-mail: kguo@lincoln.ac.uk

Tel: +44-1522-886294 Fax: +44-1522-886026

Abstract

Our visual inputs are often entangled with affective meanings in natural vision, implying the existence of extensive interaction between visual and emotional processing. However, little is known about the neural mechanism underlying such interaction. This exploratory transcranial magnetic stimulation (TMS) study examined the possible involvement of the early visual cortex (EVC, area V1/V2/V3) in perceiving facial expressions of different emotional valences. Across three experiments, single-pulse TMS were delivered at different time windows (50-150 ms) after brief 10 ms onset of face images, and participants reported the visibility and perceived emotional valence of faces. Interestingly earlier TMS at ~90 ms only reduced the face visibility irrespective of displayed expressions, but later TMS at ~120 ms selectively disrupted the recognition of negative facial expressions, indicating the involvement of EVC in the processing of negative expressions at a later time window, possibly beyond the initial processing of fed-forward facial structure information. The observed TMS effect was further modulated by individuals' anxiety level. TMS at ~110-120 ms disrupted the recognition of anger significantly more for those scoring relatively low in Trait anxiety than the high-scorers, suggesting cognitive bias influences the processing of facial expressions in EVC. Taken together, it seems that EVC is involved in structural encoding of (at least) negative facial emotional valence, such as fear and anger, possibly under modulation from higher cortical areas.

Keywords: facial expression; affective visual cue; early visual cortex; transcranial magnetic stimulation

Introduction

Visual signals in our surroundings are often associated with different emotional valences and intensities. For instance, happy faces are pleasant but angry faces are frightening visual inputs for most of us. The affective meanings embedded in such visual signals have significant impact on our visual processing capabilities, including target detection speed and accuracy, and perceptual field size (Phelps, 2006). Typically, we are more sensitive to detect fearful faces than neutral or happy faces (Yang, Zald, & Blake, 2007). With recent technical advances in cognitive neuroscience, research on when and where the neural processing of visual signals is modulated by their affective meanings in the visual pathway has attracted increasing attention.

A few functional magnetic resonance imaging (fMRI) and neurophysiological studies have indicated that the affective value of visual stimuli has modulatory influence upon neuronal activation in a range of cortical regions in the visual pathway (e.g., visual areas in occipital and temporal cortex), usually reflected by relatively enhanced neural responses for emotional relative to neutral stimuli (Vuilleumier & Driver, 2007). This is seen even as early as primary visual cortex (area V1, the first cortical stage of visual processing) (Padmala & Pessoa, 2008) with a response latency of processing fed-forward visual information (Li, Yan, Guo, & Li, 2019). However, electroencephalography (EEG) studies have argued that these affective-modulated visual neural responses, such as enhanced P1 component to affective stimuli, start at a late time window of ~120 ms suggesting feedback neural modulation processes (Batty & Taylor, 2003; Pourtois, Thut, Grave de Peralta, Michel, & Vuilleumier, 2005). It seems unclear, therefore, to what extent the emotion-modulated activities in the early visual cortex (EVC) happen at the early or late stage of visual processing (e.g., during the processing of early fed-forward or late fed-back information).

Transcranial magnetic stimulation (TMS) is a relatively reliable investigative tool to study functional connectivity for visual neurons (Walsh & Cowey, 2000). It has been argued that single-pulse TMS delivered at different time windows after the stimulus onset can transiently disrupt feedforward or feedback processing in EVC. Typically, a TMS pulse over the occipital cortex at 90-100 ms post-stimulus onset maximally suppress participants' conscious detection performance of a small visual target (e.g., grating, bar, single letter) presented within the visual hemifield contralateral to the stimulated cortical hemisphere, at a location corresponding to V1 retinotopic organization (Sack, van der Mark, Schuhmann, Schwarzbach, & Goebel, 2009; de Graaf, Cornelsen, Jacobs, & Sack, 2011; Roebuck, Bourke, & Guo, 2014). This time window is often interpreted as consistent with the activity of feedforward processing in V1 neurons (see also Kammer, 2007). In contrast, the disruption by a later TMS pulse at 100-130 ms is susceptible to attention and task demands (e.g., reducing performance for face discrimination task rather than grating detection task; de Graaf, Goebel, & Sack, 2012), suggesting this late time window may represent a recurrent process of visual information fed-back from other brain structures (de Graaf, Koivisto, Jacobs, & Sack, 2014).

It should be noted while these studies often positioned the TMS coil over the occipital cortex and aimed to target area V1 using anatomical landmark and/or phosphene localization procedures, a few studies have combined fMRI-based mapping of visual cortex with modelling of the TMS-induced electric field in the brain and argued that the actual stimulated region went beyond the targeted V1 area, also covering neighbouring and connected functional regions, such as the corresponding retinotopic area in dorsal V2 and/or V2/V3 border (Thielscher, Reichenbach, Ugurbil, & Uludag, 2010; Salminen-Vaparanta, Noreika, Revonsuo, Koivisto, & Vanni, 2012). As it is difficult to precisely localize the induced

electric field in the occipital cortex, it could be more appropriate to attribute the TMS-induced effect to the disruption of EVC (area V1/V2/V3) rather than V1 only.

Recently TMS has been applied to study the processing of affective visual cues, such as facial expressions of emotion. TMS over the right occipital face area (rOFA), an integral part of the face-processing neural network which receives both fed-forward and fed-back facial information from other face sensitive areas, at 60-100 ms post-stimulus onset impairs expression discrimination accuracy, most likely reflecting the disruption of early feedforward processing (Pitcher, Garrido, Walsh, & Duchaine, 2008). At 170-300 ms it impairs the analysis and integration of facial identity and expression cues, most likely reflecting the disruption of late feedback processing (Kadosh, Walsh, & Kadosh, 2011). It is unclear, however, whether facial expression cues could be processed or differentiated in areas earlier than rOFA in the visual pathway. In this exploratory study, we aimed to deliver single-pulse TMS over EVC at different time windows representing feedforward and feedback processing and to compare participants' expression categorization performance of face images displaying different emotional valence. The findings would help to address whether neurons in EVC (including area V1/V2/V3) show different processing speeds to affective visual signals of varying valence, and possible feedforward and feedback contribution to such affective processing.

Considering that an accurate and timely recognition of negative facial expression is biologically relevant and crucial to our survival and normal social functioning, it is not surprising that many behavioural and brain imaging studies have revealed enhanced perceptual and neural sensitivities for processing negative expressions in comparison with neutral and positive ones. Typically, angry and fearful expressions tend to pop out more easily, capture and hold attention automatically (e.g., anger superiority effect) (Hansen & Hansen, 1998; Anderson, 2005), amplify perceptual process (Öhman, Lundqvist, & Esteves,

2001), and enhance early face-specific electrophysiological responses, such as P1 and N170 event-related potential responses, even outside of attention or pre-attentively (Yang et al., 2007; Lyyra, Hietanen, & Astikainen, 2014). The replication of these findings with simplified schematic line-drawing faces instead of real face images (but not with the inverted schematic faces) further indicated that 'anger superiority effect' is likely caused by semantic differences in facial emotional valence rather than visual changes in local facial structures or features between different expressions (Öhman et al., 2001; Horstmann, 2007).

Although these facial emotional valence-modulated neural responses are commonly observed in P1 and N170 components which are likely generated in extrastriate cortex (e.g., Yang et al., 2007; Lyyra et al., 2014), a couple of studies have reported that fearful faces could elicit larger C1 component, which is the earliest visually evoked potential (~60-90 ms post-stimulus onset) and may be generated in V1, than happy faces (Pourtois, Grandjean, Sander, & Vuilleumier, 2004; Zhu & Luo, 2012). However, the valence-modulated C1 responses have not been consistently observed across previous studies and may be related to the systematic biases in data filtering (Acunzo, Mackenzie, & van Rossum, 2012) and the attentional process involved in the task (Slotnick, 2018), such as spatial orienting (Pourtois et al., 2004) and executive attention (Zhu & Luo, 2012).

Nevertheless, given these enhanced C1, P1 and N170 responses to negative facial expressions reported in previous research, the involvement of EVC in the processing of facial expressions might happen at a time window earlier than the typical response latencies of P1 and N170 components (~100-120 ms and ~170 ms, respectively). Therefore in our first exploratory study, we examined whether the delivery of TMS over EVC at early time windows (50-120 ms) could selectively disrupt the processing of negative facial expressions.

Experiment 1: TMS at early time windows

Experimental procedures

Participants

Sixteen Caucasian adult participants (12 males), with mean age of 20 ± 0.49 (Mean ± SEM) years old, took part in Experiment 1. Three more participants were initially tested but were later excluded from data analysis due to failure to induce reliable phosphene and/or frequent head movements during the testing (hence unreliable cortical TMS stimulation location). This sample size was based on previous research in the same field and was comparable to those published reports (e.g., de Graaf et al., 2011, 2014; Roebuck et al., 2014). The suitability of the sample size was confirmed by power analysis using G*power software (Faul, Erdfelder, Lang, & Buchner, 2007). A sample of 16 participants would be large enough to detect a typical effect size ($\eta_p^2 = 0.3$) with a power of 0.95 at alpha level 0.05 in a repeated measures design with 9 TMS time windows to estimate the effect of TMS on visual target detection.

All participants (including those in Experiment 1, 2 and 3) had normal or corrected-to-normal visual acuity and reported no history of neuropsychiatric illness or epilepsy. Prior to each experiment, the research purpose, experimental task and procedure had been explained to the participants, and written informed consent was obtained from each of them. The Ethical Committee in School of Psychology, University of Lincoln, approved this study, and all procedures complied with the British Psychological Society "Code of Ethics and Conduct", and with the World Medical Association Helsinki Declaration as revised in October 2008.

Visual stimuli and TMS set-up

Grey-scale western Caucasian face images, consisting of three female and three male models, were selected from the Karolinska Directed Emotional Faces CD ROM (Lundqvist, Flykt, & Öhman, 1998). Each of these models posed happy, neutral and angry facial expressions in full frontal view. Although they may have real-world limitations, and

categorization performance for some expressions could be subject to culture influence, these well-controlled face images were chosen for their comparability and universality in transmitting facial expression signals, at least for our observer group (Caucasian young adults). The faces were processed in Adobe Photoshop to remove external facial features (e.g., hair) and to ensure a homogenous background, brightness and face size (54 × 71 pixel, 2 × 2.63°). As a result, 18 expressive face images were generated for the testing session (3 expressions × 6 models, see Fig. 1 for examples).

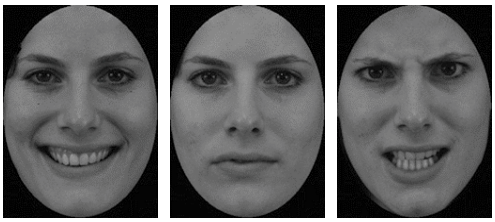

Figure 1. Examples of a female face image presented with happiness, neutral, and anger facial expressions.

The face images were presented through a ViSaGe Graphics system (Cambridge Research Systems) and displayed on a non-interlaced gamma-corrected monitor (100 Hz frame rate, 40 cd/m^2 background luminance, 1024 × 768 pixel resolution, 33 × 24° at the viewing distance of 70 cm, Mitsubishi Diamond Pro 2070SB). During the presentation, the centre of the face image was at 1.5° to the right of a small central fixation point (FP, 0.2° diameter, 10 cd/m^2).

TMS was delivered by using a 70 mm figure-of-eight coil (Medtronic MC-B70 coil) through a Medtronic MagPro X100. The coil location and TMS intensity was determined for each participant prior to the testing session. Initially, the TMS intensity was set at 50% of the maximum output, and the coil was placed ~2 cm above and 1 cm left of the inion, with the main axis of the coil oriented parallel to the sagittal plane. After fixating on the FP, a TMS pulse was administered manually, and the participants reported whether they experienced a phosphene within a faint thin-line oval which corresponded to the location of the face image

presentation. The location of the coil and TMS intensity was adjusted according to the reported percept until a reliable phosphene was perceived. The TMS intensity was then reduced to the phosphene detection threshold, defined as the intensity at which the phosphene was reported two out of five TMS pulses. Finally, the TMS intensity for the main experiment was set at 120% of the phosphene detection threshold to ensure a reliable cortical stimulation and disruption over EVC (de Graaf et al., 2012). Across all the participants, the average TMS intensity used during the testing was 69% ± 1.42 (Mean ± SEM).

Procedure

To control for artefacts associated with TMS (e.g., auditory click sound, mechanical tapping, and muscle contraction) which may disrupt participants' attention and affect their expression categorization performance, participants took part in two separate testing sessions: a TMS session in which the TMS pulses were administered on the left occipital cortex at a location corresponding to the face image onset, and a control (sham) session in which the same intensity TMS pulses were administered on the right occipital cortex (task unrelated area) which mirrored the stimulation location on the left occipital cortex. Except for the coil location, all the other experimental parameters (e.g., coil orientation, TMS time windows and intensity) and procedures were the same between TMS and control sessions. The order of the testing sessions was counter-balanced across the participants.

During the experiments, participants sat in a quiet, darkened room and viewed the display binocularly with support of a chin rest. No earplugs were applied. The trial was started by a 350 Hz warning tone lasting 150 ms followed by the presentation of a central FP for 1000 ms. A face image with happy, neutral or angry expression was then presented for 10 ms. Single-pulse TMS was administered at one of nine stimulus onset asynchrony time windows (i.e. at 50, 60, 70, 80, 90, 100, 110 or 120 ms post-face onset, plus no-TMS condition). The participants were instructed to maintain fixation of the FP throughout the

trial, and verbally report (or guess if it is necessary) the perceived facial expression valence (3-alternative forced choice: positive, neutral, and negative) and the perceived face image visibility on a 5-point scale, in which 1 represents "not visible at all" and 5 represents "clearly visible for all image details". No feedback was given. The trial interval was set to 1500 ms. Each participant was tested for one sham/control block and two TMS blocks (162 trials per block, 18 face images (6 face identities for each of three expressions) × 9 TMS conditions (8 TMS time windows between 50 and 120 ms + 1 no-TMS condition)). Therefore, 12 trials were presented for each facial expression at each TMS condition over two TMS blocks. Prior to the formal test, the participants were given a training session (normally 20 trials) to familiarise with the task.

All the collected data were analyzed off-line. A series of repeated measures analysis of variance (ANOVAs) were conducted to examine the effect of TMS on participants' facial expression valence recognition accuracy and face image visibility rating. For each ANOVA, Greenhouse–Geisser correction was applied where sphericity was violated, and a Bonferroni adjustment was made for post-hoc multiple comparisons.

Results and discussion

A 9 (TMS conditions: no-TMS, TMS at 50, 60, 70, 80, 90, 100, 110 and 120 ms) × 3 (facial expressions) ANOVA was conducted to examine to what extent TMS at different time windows would affect participants' image visibility ratings across faces of different emotional valence (Fig. 2A). The analysis revealed significant main effect of TMS condition ($F(4.21,63.1) = 3.15$, $p = 0.02$, $\eta_p^2 = 0.17$) with TMS delivered at 90 ms inducing slightly lower face image visibility rating in comparison with the no-TMS condition ($p < 0.01$), and a significant main effect of expression ($F(2,30) = 5.93$, $p = 0.01$, $\eta_p^2 = 0.28$) with happy faces attracting higher visibility rating than angry faces ($p = 0.01$) but not than neutral faces ($p = 0.09$). While there was no significant TMS condition × expression interaction ($F(16,240) = 1$,

p = 0.46, η_p^2 = 0.06), Figure 2A indicates that the interaction effect might lie beyond the time-window studied. TMS delivered at 120 ms showed a tendency to reduce visibility rating only for angry faces in comparison with no-TMS condition (2-tailed t-test, $t(15)$ = 2.88, p = 0.01, 95% CIs [2.33, 15.59], Cohen's d = 0.75).

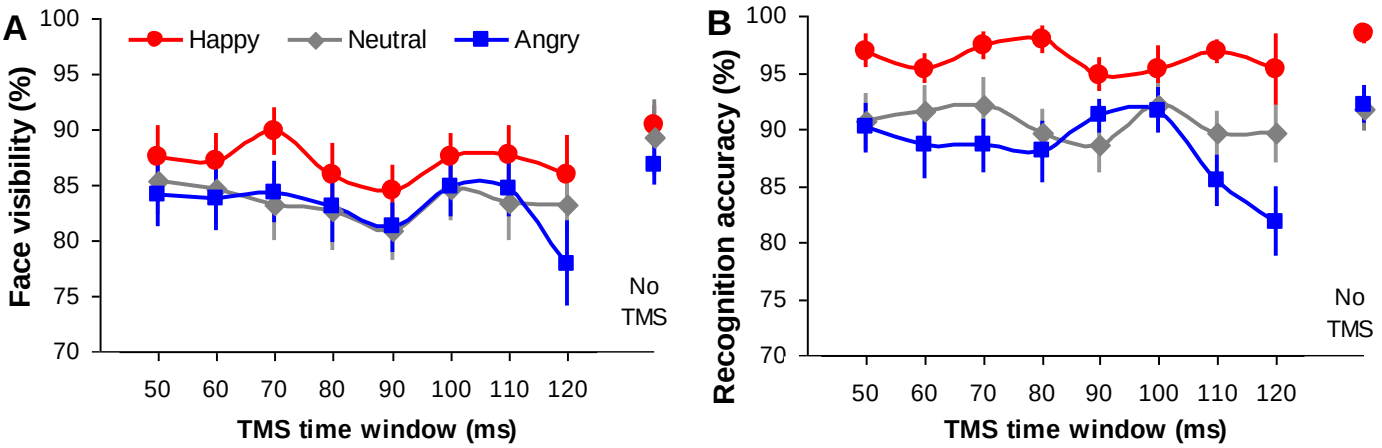

Figure 2. Effect of TMS at different time windows on participants' image visibility rating (A) and emotional valence recognition accuracy (B) of faces displaying happy, neutral and angry expressions. Error bars represent SEM.

Another 9 (TMS conditions) × 3 (facial expressions) ANOVA was also conducted to examine to what extent TMS at different time windows would affect participants' valence recognition accuracy for faces of different expressions (Fig. 2B). The analysis revealed significant main effect of expression ($F(2,30)$ = 11.92, p < 0.001, η_p^2 = 0.43) with higher recognition accuracy for happy than angry or neutral expression (all ps < 0.01), but non-significant main effect of TMS condition ($F(8,120)$ = 1.83, p = 0.08, η_p^2 = 0.11) or TMS condition × expression interaction ($F(16,240)$ = 1.13, p = 0.32, η_p^2 = 0.07). However, Figure 2B indicates a clear tendency that TMS at a later time window (110 and 120ms) might selectively reduce participants' valence recognition performance for negative (angry) faces in comparison with no-TMS condition (2-tailed t-test, 110 ms: $t(15)$ = 3.31, p = 0.005, 95% CIs [2.41, 11.13], Cohen's d = 0.87; 120 ms: $t(15)$ = 3.18, p = 0.006, 95% CIs [3.44, 17.39], Cohen's d = 1.07).

In contrast, for a given facial expression TMS delivered on the right occipital cortex (sham/control session) across all the time windows showed no impact on participants' face image visibility rating (TMS condition: $F(8,120) = 1.34$, $p = 0.23$, $\eta_p^2 = 0.08$; TMS condition × expression: $F(16,240) = 1.56$, $p = 0.08$, $\eta_p^2 = 0.09$) and emotional valence recognition performance (TMS condition: $F(8,120) = 0.36$, $p = 0.94$, $\eta_p^2 = 0.02$; TMS condition × expression: $F(16,240) = 0.81$, $p = 0.67$, $\eta_p^2 = 0.05$). When examining TMS vs Sham TMS on face visibility and valence recognition accuracy, 2 (sessions: TMS vs Sham TMS) × 9 (TMS conditions) × 3 (facial expressions) ANOVA only revealed significant interaction between sessions and TMS conditions on face visibility ($F(8,120) = 2.31$, $p = 0.03$, $\eta_p^2 = 0.13$), but did not reveal any main effect of sessions and its interaction with TMS conditions and/or facial expressions on valence recognition accuracy (all $ps > 0.05$). Given that in this exploratory study we used multiple TMS conditions and possible TMS disruption is expression-specific and timing-restricted (~120 ms, Fig. 2B), it is possible that the lack of statistical power accounts for the lack of session-specific effect on valence recognition accuracy. Nevertheless, across all the presented expressions, compared with sham/control session, in TMS sessions TMS at 90 ms tended to reduce participants' face image visibility rating ($t(47) = 1.98$, $p = 0.027$, 95% CIs [-0.05, 7.05], Cohen's $d = 0.28$; Fig. 3A), and TMS at 120 ms tended to reduce their emotional valence recognition performance ($t(47) = 2.05$, $p = 0.023$, 95% CIs [0.08, 8.95], Cohen's $d = 0.38$; Fig. 3B).

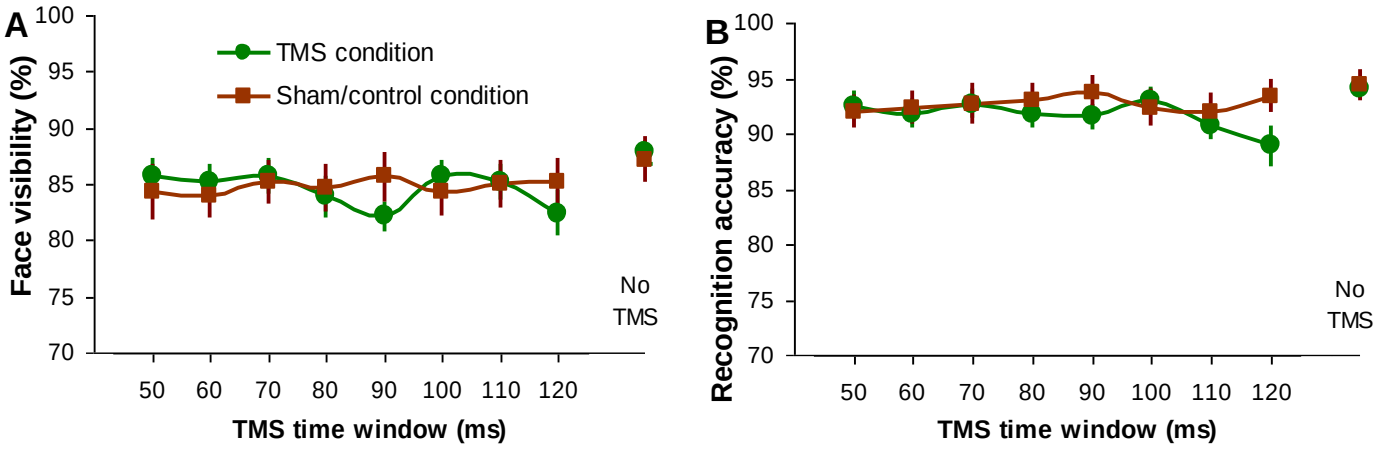

Figure 3. Effect of TMS delivered at left (TMS session) and right occipital cortex (sham/control session) on participants' image visibility rating (A) and emotional valence recognition accuracy (B) of faces displaying happy, neutral and angry expressions. Error bars represent SEM.

Clearly, TMS over EVC at the time window of processing feedforward information (~90 ms) appeared to disrupt face image visibility irrespective of the displayed facial expressions, but had little detrimental effect on facial valence judgement; whereas TMS at 120 ms appeared to have a tendency to selectively decrease both face image visibility rating and valence recognition for angry faces alone, implying that early visual neural responses to faces containing negative emotional information might be modulated at a later time window. This possibility was examined in details in Experiment 2 in which we extended the TMS time window from 50-120 ms to 90-150 ms.

Experiment 2: TMS at late time windows

Experimental procedures

Eleven Caucasian adult participants (7 males, 21 ± 0.56 years old) took part in Experiment 2. Two more participants were initially tested but were later excluded from data analysis due to frequent head movements during the testing. This sample size was comparable to previous research in the same field (e.g., de Graaf et al., 2011; Roebuck et al.,

2014) and was further confirmed by power analysis (Faul et al., 2007). A sample of 9 participants would be large enough to detect the maximum effect size (η_p^2 = 0.43) observed in Experiment 1 with a power of 0.95 at alpha level 0.05 in a repeated measures design with 8 TMS time windows to estimate the effect of TMS on visual target detection.

The visual stimuli, TMS set-up and experimental procedure were identical to those used in Experiment 1 except that (1) in Experiment 2, single-pulse TMS was administered at one of eight conditions (i.e. at 90, 100, 110, 120, 130, 140, or 150 ms post-face onset, plus a no-TMS condition), (2) no sham/control session was used in Experiment 2. Across all the participants, the average TMS intensity used during the testing was 73% ± 1.87.

Results and discussion

To examine how face image visibility was modulated by TMS at the later time windows (Fig. 4A), 8 (TMS conditions: no-TMS, TMS at 90, 100, 110, 120, 130, 140 and 150 ms) × 3 (facial expressions) ANOVA revealed a significant main effect of TMS condition (F(3.34,33.42) = 5.11, p = 0.004, η_p^2 = 0.34) with TMS delivered at 90 ms inducing slightly lower face image visibility rating in comparison with no-TMS conditions across all facial expressions (p < 0.001), and significant main effect of expression (F(2,20) = 10.32, p = 0.001, η_p^2 = 0.58) with happy faces attracting higher visibility rating than angry faces (p = 0.009) but not than neutral faces (p = 0.06). Although there was no significant TMS condition × expression interaction (F(14,140) = 0.92, p = 0.54, η_p^2 = 0.08), planned comparison revealed that in comparison with the no-TMS condition, TMS delivered at 120 ms tended to reduce visibility for angry faces (t(10) = 3.22, p = 0.009, 95% CIs [3.50, 19.23], Cohen's d = 0.76). All these findings were in agreement with those observed in Experiment 1.

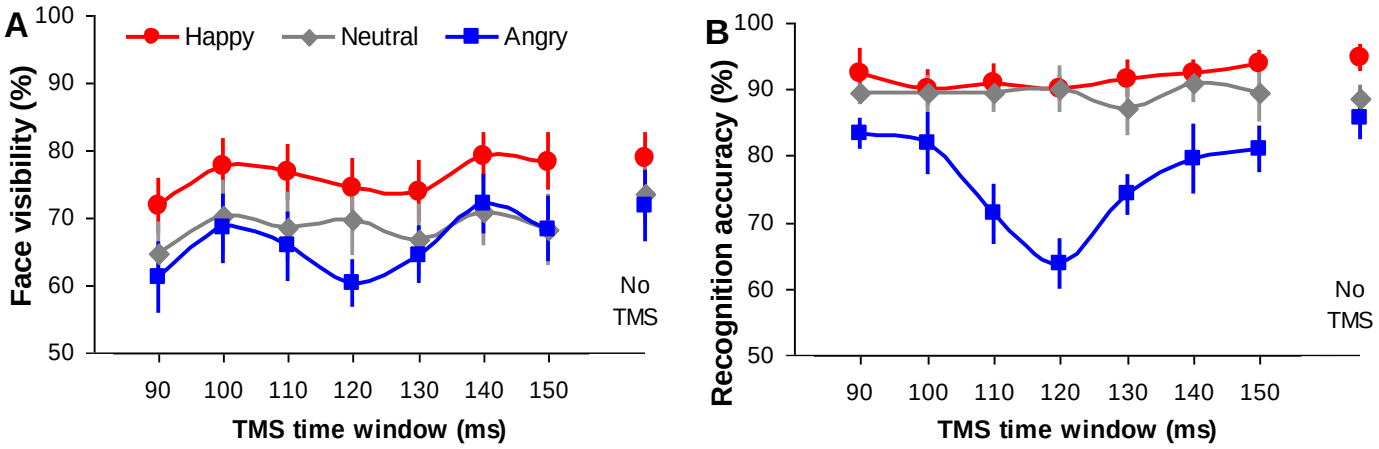

Figure 4. Effect of TMS at different time windows on participants' image visibility rating (A) and emotional valence recognition accuracy (B) of faces displaying happy, neutral and angry expressions. Error bars represent SEM.

For facial valence recognition accuracy (Fig. 4B), 8 (TMS conditions) × 3 (facial expressions) ANOVA revealed significant main effect of expression ($F(2,20) = 11.11$, $p = 0.001$, $\eta_p^2 = 0.53$) with lower recognition accuracy for angry than for happy ($p = 0.006$) or neutral expression ($p = 0.03$), and significant main effect of TMS condition ($F(7,70) = 4.15$, $p = 0.01$, $\eta_p^2 = 0.29$) and TMS condition × expression interaction ($F(14,140) = 2.75$, $p = 0.001$, $\eta_p^2 = 0.22$). Specifically, in comparison with other time windows and no-TMS condition, TMS at 110-130 ms gradually disrupted the recognition of angry expression with the lowest recognition accuracy at 120 ms (all *ps* < 0.05). On the other hand, the same TMS pulse delivered at these time windows had negligible influence on the recognition of happy and neutral expressions (all *ps* > 0.05).

The combined findings from Experiment 1 and 2 have suggested that in EVC the facial expressions of emotion are processed later than the facial structures, and are subject to valence-dependent process disruption. This view is supported by the observation that TMS at ~90 ms only reduced face image visibility across all expressions but had no impact on facial emotional valence recognition, whereas later TMS at ~120 ms selectively disrupt both the visibility and the recognition of negative expressions but had no impact on the recognition of

positive and neutral ones. It seems that early visual neural responses to affective visual cues were modulated at a later time window, possibly beyond the initial detection or processing of fed-forward visual information.

If EVC is indeed involved in the processing of affective facial information, it is plausible that its neural responses could be further subject to the influence of cognitive bias associated with facial expression perception. In other words, the affective state of an individual may itself bias early visual neural processing of emotional faces. This possibility was examined in details in Experiment 3.

Experiment 3: TMS at late time windows for participants with varying anxiety levels

It is well-established that anxiety is associated with a cognitive bias in the processing of emotional information, such as allocating cognitive resources selectively to threat-related information (Bar-Haim, Lamy, Pergamin, Backermans-Kranenburg, & Van Ijzendoorn, 2007) and interpreting ambiguous or neutral information as negative and threatening (Calvo & Castillo, 2001). When categorizing facial expressions, anxious individuals show higher perceptual sensitivity to threatening faces (Fox, 2002; Staugaard, 2010) and higher accuracy in identifying negative expressions such as anger and fear (Hunter, Buckner, & Schmidt, 2009; Doty, Japee, Ingvar, & Ungerleider, 2013). However, the neural processes underlying the generation of these cognitive biases remain largely unknown. For instance, it is unclear whether cognitive bias in anxious individuals could be reflected in EVC's involvement in the processing of negative facial expressions.

Furthermore, different subtypes of anxiety may have different impact on the recognition of different facial expressions. While trait anxiety, a relatively stable anxiety-proneness that reflects individuals' tendency to perceive threats, stress and danger (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), is associated with increased

accuracy in identifying fear and anger expressions (Hunter et al., 2009; Surcinelli, Codispoti, Montebarocci, Rossi, & Baldaro, 2006; Doty et al., 2013); state anxiety, an emotional state felt in a particular situation or about a particular event (Spielberger et al., 1983), is associated with decreased accuracy in recognizing common facial expressions except for sadness (Attwood et al., 2017). Furthermore, the prolonged state anxiety measured by Beck Anxiety Inventory, a relatively objective measurement of anxiety symptoms that have occurred during the past month (Beck, Epstein, Brown, & Steer, 1988), is coupled with enhanced categorization accuracy for all common facial expressions (Green & Guo, 2018). Hence it is plausible that EVC may contribute differently to the processing of facial expressions in individuals with different anxiety subtypes.

To explore these research questions, in Experiment 3 we measured participants' trait and state anxiety level using the classical State-Trait Anxiety Inventory which consists of 40 questions on a 4-point Likert scale self-report basis (Spielberger et al., 1983) and the Beck Anxiety Inventory which includes 21 anxiety symptoms and allows the participant to rate to what level each symptom has bothered them during the past month (Beck et al., 1988). The Beck Anxiety Inventory was chosen because of its minimised overlap between anxiety and depression measurement (e.g., state–trait anxiety inventory tends to be highly correlated with depression), high level of internal consistency and high discriminant validity when used in a non-clinical sample of anxiety research (Ayala, Vonderharr-Carlson, & Kim, 2005). We then delivered single-pulse TMS over EVC at different time windows to examine to what extent individuals with different anxiety subtypes responded differently to negative facial expressions, such as fear and anger.

Experimental procedures

Forty-four Caucasian adult participants (20 males, 21 ± 0.35 years old) took part in Experiment 3. Five more participants were initially tested but were later excluded from data

analysis due to failure to induce reliable phosphenes and/or frequent head movements during the testing. The suitability of this sample size was confirmed by power analysis. A sample of 18 participants would be large enough to detect an average effect size (η_p^2 = 0.3) observed in Experiment 2 with a power of 0.95 at alpha level 0.05 in a repeated measures design with 8 TMS time windows to estimate the effect of TMS on visual target detection.

Grey-scale western Caucasian face images, consisting of three female and three male models, were selected from the Karolinska Directed Emotional Faces CD ROM (Lundqvist et al., 1998). Each of these models posed happy, fear and angry facial expressions in full frontal view. All the images were processed in the same way as in Experiment 1.

The TMS set-up and experimental procedure were identical to those used in Experiment 2. Across all the participants, the average TMS intensity used during the testing was 68% ± 0.7. Either before or after the TMS testing, the participants were required to complete the State-Trait Anxiety Inventory and the Beck Anxiety Inventory.

Results and discussion

In Experiment 3, the analysis was focused on the effect of TMS on facial expression recognition accuracy. Across all the participants, 8 (TMS conditions: no-TMS, TMS at 90, 100, 110, 120, 130, 140 and 150 ms) × 3 (facial expressions) ANOVA revealed significant main effect of expression ($F(1.53,65.97) = 32.72$, $p < 0.001$, $\eta_p^2 = 0.43$; Fig. 5) with higher recognition accuracy for happy than for fear ($p < 0.001$) or angry expression ($p < 0.001$), and significant main effect of TMS condition ($F(7,301) = 3.08$, $p = 0.004$, $\eta_p^2 = 0.07$) and TMS condition × expression interaction ($F(9.38,403.51) = 3.61$, $p < 0.001$, $\eta_p^2 = 0.08$). Specifically, in comparison with other time windows and the no-TMS condition, TMS at 110-130 ms disrupted the recognition of fear with the lowest recognition accuracy at 120ms (all *ps* < 0.05); whereas TMS at 110, 130 and 150 ms disrupted the recognition of anger (all

ps < 0.05). On the other hand, the TMS pulses delivered at these time windows had negligible influence on the recognition of happy faces (all *ps* > 0.05).

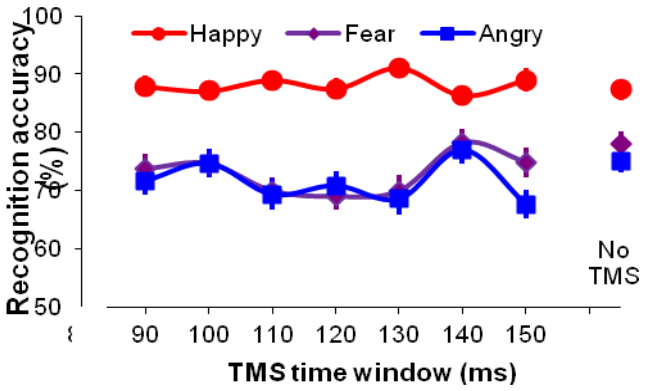

Figure 5. Effect of TMS at different time windows on participants' facial expression recognition accuracy of faces displaying happy, fear and angry expressions. Error bars represent SEM.

We then examined to what extent individuals' anxiety level impact on their fear and anger recognition under TMS conditions. To control for individual differences in the baseline expression recognition performance at the no-TMS condition, we calculated fear and anger recognition index for each participant under TMS conditions, in which expression recognition accuracy at each TMS delivery time window was divided by recognition accuracy at the no-TMS condition. Consequently, an index of 1 indicates TMS delivered at a given time window has no impact on expression recognition in comparison with the no-TMS condition, whereas an index smaller than 1 indicates TMS would disrupt expression recognition.

Table 1. Pearson correlation analysis between anxiety score and fear and anger recognition index at different TMS time windows.

		Trait Anxiety	State Anxiety	Beck Anxiety
Fear	90 ms	0.14 (0.38)	-0.01 (0.95)	0.19 (0.23)
	100 ms	0.05 (0.74)	0.05 (0.74)	0.14 (0.35)
	110 ms	0.20 (0.20)	0.06 (0.68)	0.25 (0.11)
	120 ms	0.10 (0.50)	0.08 (0.60)	0.03 (0.83)
	130 ms	0.10 (0.51)	0.07 (0.63)	0.11 (0.47)
	140 ms	0.02 (0.88)	0.09 (0.54)	0.11 (0.46)
	150 ms	0.08 (0.62)	0.08 (0.61)	0.17 (0.26)
Anger	90 ms	0.33 (0.03)*	0.14 (0.38)	0.32 (0.03)*
	100 ms	0.23 (0.14)	0.21 (0.17)	-0.05 (0.73)
	110 ms	0.45 (0.002)**	0.33 (0.03)*	0.19 (0.23)

120 ms	0.50 (0.001)**	0.38 (0.01)*	0.26 (0.09)
130 ms	0.40 (0.007)**	0.29 (0.05)*	0.24 (0.12)
140 ms	0.27 (0.07)	0.22 (0.15)	0.09 (0.56)
150 ms	0.33 (0.03)*	0.30 (0.05)*	0.19 (0.21)

Note: Values in the table represent *r* value (*p* value). *$p<0.05$, **$p<0.01$.

Across our participants, the two-tailed Pearson correlation analysis between anxiety subtype score (Trait, State and Beck anxiety) and fear or anger recognition index revealed an anxiety-dependent influence on the recognition of angry expressions (Table 1). Specifically, there was no significant correlation between anxiety subtype and fear recognition index across different TMS time windows (all *ps* > 0.05), indicating the observed TMS disruption on the recognition of fear (Fig. 5) was not susceptible to individual's anxiety level and measurement type. However, both Trait and State anxiety measurements were positively correlated with anger recognition index, especially when TMS was delivered at 110 – 130 ms (all *ps* < 0.05), indicating greater TMS disruption on recognizing angry faces for those scoring lower on Trait and State anxiety. Beck anxiety, on the other hand, was only correlated with anger recognition index for TMS at 90 ms ($p = 0.03$).

Given that the measurements of different anxiety subtypes were positively correlated with each other (Trait vs State: $r = 0.75$, $p < 0.001$; Trait vs Beck: $r = 0.63$, $p < 0.001$; State vs Beck: $r = 0.46$, $p = 0.002$), we then conducted Partial correlation analysis to clarify different anxiety subtypes' independent contribution. After controlling for State anxiety, Trait anxiety was positively correlated with anger recognition index at 90 ms TMS ($r = 0.36$, $p = 0.02$), 110 ms TMS ($r = 0.33$, $p = 0.03$) and 120 ms TMS ($r = 0.36$, $p = 0.02$). There was no other significant correlation between a given anxiety subtype and fear or anger recognition index at various TMS time windows after controlling for other anxiety subtypes (all *ps* > 0.05). Taken together, it seems that the TMS disruption on fear recognition was independent of individual's Trait, State or Beck anxiety level, but the TMS disruption on anger

recognition was modulated by Trait anxiety with low-scoring individuals showing larger TMS disruption at 90,110 and 120 ms.

General discussion

The combined novel findings from Experiment 1 and 2 have revealed that earlier TMS over EVC at ~90 ms reduced face image visibility rating but had no impact on facial emotional valence recognition, whereas later TMS at ~120 ms selectively disrupted both the visibility and the recognition of negative expressions but had no impact on the recognition of positive and neutral ones, suggesting that the facial expressions are processed later than the facial structures in EVC. It seems that early visual neural responses to affective facial cues are involved and so can be modulated at a later time window, possibly beyond the initial detection or processing of fed-forward facial structural information. This observation is also broadly in agreement with Bruce and Young's functional model of face processing (Bruce & Young, 2012), in which facial expression analysis is conducted after the initial stage of facial structural encoding (i.e. view-centred descriptions).

Furthermore, the observed TMS effects at different time windows (90 ms vs 120 ms) suggest that different neural mechanisms may be involved in the processing of facial structure and facial emotional valence in EVC. Previous visual masking studies have reported that TMS over EVC is likely to induce a two-stage suppression effect (i.e. decreased visual target detection or discrimination performance at two different time widows), indicating a two-stage visual process in which the early time window (90-100 ms) may represent a feedforward process of visual information relatively independent of stimuli, tasks and context; whereas the later time window (100-130 ms) may represent a recurrent process of visual information fed-back from other brain structures and potentially susceptible to attention and task demands (for a review, see de Graaf et al., 2014). It is plausible that the

observed TMS-induced reduction in face visibility rating at ~90 ms and in negative expression recognition at ~120 ms might reflect the feedforward and feedback processes of different facial cues in EVC, respectively.

Interestingly, TMS at ~120 ms selectively disrupted the recognition of negative expressions but had no impact on the recognition of positive ones, suggesting that the processing of negative expressions is more susceptible to the TMS disruption over EVC even though positive ones tend to attract higher visibility rating and recognition accuracy (Fig. 2 and 4). It has been well-established that among common facial expressions (happy, sad, angry, fear, surprise and disgust), recognition of happiness is associated with the highest accuracy and fastest reaction time, and is the least susceptible to expression intensity decline and image quality distortion (Guo, 2012; Guo, Soornack, & Settle, 2019), which is probably due to happy expression being more distinctive than other expressions (by containing fewer overlapping features with the others) and our prior experience in processing different expressions (e.g., happiness is the first expression to reach adult-level recognition accuracy in children's development; Rutter et al., 2019). Consequently the recognition of happiness might be less cognitively demanding and lead to higher visibility rating and less susceptible to the TMS disruption observed in our study.

Even though anger and fear are recognized with relatively lower accuracy and longer reaction time than happy expression (Guo, 2012), they tend to be detected quicker (but not necessarily recognized correctly at categorical level) and initiate neural process earlier than happy expression (Yang et al., 2007; Lyyra et al., 2014). The observed selective TMS disruption at ~120 ms on the recognition of negative expressions might also be associated with the difference in processing speed between negative and positive expressions in EVC. Previous studies have commonly reported that negative expressions, rather than positive ones, would enhance early visual and face-specific electrophysiological responses, such as

C1, P1 and N170 event-related potential responses (e.g., Pourtois et al., 2004; Yang et al., 2007; Zhu & Luo, 2012; Calvo & Beltran, 2013; Lyyra et al., 2014), implying a relatively earlier processing of negative than positive expressions. As we did not observe a disruption of positive expressions at a later time point within the tested TMS time windows (90-150 ms), future research could further extend the TMS time range (e.g., to ~250 ms).

Both neuropsychological and brain imaging studies have suggested a crucial role of amygdala in processing negative facial expressions. Typically, patients with bilateral amygdala lesions would demonstrate impaired recognition of fearful expressions (e.g., Adolphs, Tranel, Damasio, & Damasio, 1994), and healthy participants would show enhanced neural activities in amygdala when viewing fearful and angry expressions (e.g., Gur et al., 2002). The extensive connections between amygdala and visual cortex, including area V1 (Pessoa & Adolphs, 2010; Amaral, Behniea, & Kelly, 2003), would enable the facial emotional information processed in amygdala to be projected to various visual areas. Brain images studies have observed that amygdala could modulate neural activities in other cortical neural substrates, such as inferior temporal cortex (Vuilleumier & Pourtois, 2007; Hadj-Bouziane et al., 2012), whilst assessing the biological significance of emotional faces. In light of this, it is plausible that the affective information of negative facial valence is projected from amygdala to EVC or from amygdala to higher cortical areas and then to EVC, and consequently modulate early visual neural processing of expressive faces after initial facial structure encoding. Indeed, recent studies have observed that facial expression discrimination performance could be impaired by TMS over rOFA at 60-100 ms (Pitcher et al., 2008) which is earlier than ~120 ms over EVC observed in this study, and different facial expression images (e.g., happy vs fearful faces) could induce slightly different neural activation patterns in V1 in an expression categorization task when compared with a face gender or identity discrimination task (Petro, Smith, Schyns, & Muckli, 2013; Dobs, Schultz, Bülthoff, &

Gardner, 2018; Greening, Mitchell, & Smith, 2018), suggesting that EVC might receive the processed facial emotional information from higher cortical 'face processing' areas (e.g., rOFA, superior temporal sulcus, lateral fusiform gyrus).

This observed time window (~120 ms) of processing affective visual information in EVC is in agreement with those observed in fear conditioning studies. When learning an association between a neutral stimulus with an aversive stimulus, such as pairing human faces with noxious odour, a robust learning-related brain activation enhancement is often reported in extrastriate regions in EEG or MEG studies (Pizzagalli, Greischar, & Davidson, 2003; Dolan, Heinze, Hurlemann, & Hinrichs, 2006; Steinberg et al., 2012), indicating that EVC has the capacity to respond to the affective content associated with the current visual inputs at ~120 ms.

One novelty in this study is that individuals' anxiety level could affect their facial expression recognition performance under TMS conditions. Across all the participants, TMS over EVC at ~110-130 ms disrupted the recognition of both fear and anger expressions, and the disruption on fear recognition was independent of individual's Trait, State and Beck anxiety measurements. The disruption on anger recognition, on the other hand, was modulated by individual's Trait anxiety level with the low-scorers being more susceptible to TMS disruption than the high-scorers. This difference between high- and low-scorers might be caused by anxiety-related modulation in expression recognition. Previous studies have reported higher detection sensitivity and higher recognition accuracy for angry faces in people scoring high in Trait anxiety (Surcinelli et al., 2006; Doty et al., 2013; Attwood et al., 2017). It is plausible that under TMS condition the high-scorers could still recognize degraded anger expression or are biased to interpret ambiguous expression as anger which leads to fewer 'missed' trials in the presentation of negative expressions. Consequently, the

recognition accuracy of anger expression was less reduced by TMS over EVC between 110 and 130 ms in the high- rather than low-scorers in anxiety measurements.

Alternatively, as anxious individuals often show stronger neural activation in amygdala and pulvinar when processing negative facial expressions (Steuwe et al., 2014), they might reply more on these subcortical structures for expression perception. Consequently, their expression recognition accuracy was less susceptible to TMS disruption over EVC. It would be interesting to disentangle or quantify the contribution of these two potential mechanisms underlying the observed TMS modulation in future research. Furthermore, for the low-scorers in Trait anxiety, TMS showed a detrimental effect on recognizing anger expression but not on recognizing fear expression, suggesting that EVC may have anxiety-modulated involvement in the perception of anger and fear.

It should be noted that our reported TMS modulation is based on the data from a relatively small group of young, healthy university students. It will be interesting to replicate this research with a large dataset, including participants of varying age and mental health profile (e.g., people with various anxiety disorders, such as social anxiety disorder, specific phobia, and generalized anxiety disorder). Furthermore, it remains to be seen to what extent the current findings can be generalized to the processing of other types of affective visual inputs, such as those natural and social scenes of varying valence and arousal level in the International Affective Picture System.

Nevertheless, the current study furthers our understanding of interaction between visual and emotional processing. We observed that TMS over EVC at ~120 ms selectively disrupted the recognition of negative facial expressions, suggesting that EVC is involved in the processing of affective facial cues and that its neural responses to negative cues were modulated at a time that is likely to be beyond the initial detection or processing of fed-forward facial structural information. The observed TMS effect was further modulated by

individuals' anxiety level with stronger disruption for those scoring relatively low in Trait anxiety, implying cognitive bias can affect the processing of face emotional valence in EVC. These extensive interactions between visual and emotional information among both early and later stages of the visual pathway suggest that vision and emotion are less decomposable, and perhaps function through interaction among multiple brain regions rather than a few specific structures.

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